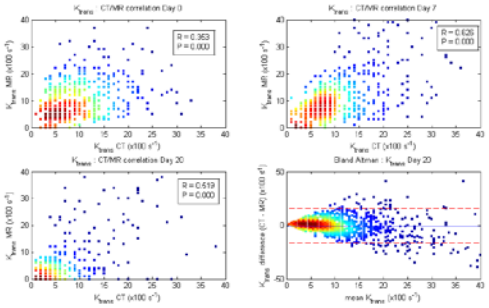

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Focal adhesion signaling and therapy resistance in cancer
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Purpose: Intrinsic and acquired resistance of tumor cells to therapy originates from multiple avenues. One avenue includes extracellular matrix (ECM) and proteins that facilitate cell interaction with ECM. These focal adhesion (FA) proteins coalesce at specific membrane sites as large multiprotein complexes functioning as signaling hubs and structural nexus. Molecular targeting of various FA proteins has shown promising preclinical data. Even more interesting are rather recent findings about activation of prosurvival bypass signaling under specific inhibition of integrins and their dependence on ECM stiffness.
Materials/methods: Different tumor models were investigated such as head and neck, pancreatic ductal carcinoma, glioblastoma. We performed a systematic targeting of FA proteins using siRNA or antibodies where applicable. In-vitro and in-vivo survival assays and a variety of mechanistic studies were conducted.
Results: To date, integrins turned out as most promising druggable candidates. Most interesting, molecular targeting generally showed to prominently induce unfavorable prosurvival signaling. Multitargeting strategies were successful to abrogate this bypass signaling and optimize radiochemosensitization.
Conclusions: Integrins and other FA proteins are promising cancer targets. Identification of underlying mechanisms is still the needle eye. From our data, multitargeting approaches on top of conventional radiochemotherapy look beneficial as specific tumor cell functions can be inhibited.

Keywords:
Focal adhesions, resistance, bypass signaling

References:
[1] Eke I, Deuse Y, Hehlgans S, Gurtner K, Krause M, Baumann M, Shevchenko A, Sandfort V, Cordes N. ß1 integrin/FAK/Cortactin signaling is essential for human head and neck cancer resistance to radiotherapy. J Clin Invest, 2012, 122(4):1529-40
[2] Eke I, Schneider L, Förster C, Zips D, Kunz-Schughart LA, Cordes N. EGFR/JIP-4/JNK2 signaling attenuates Cetuximab-mediated radiosensitization of squamous cell carcinoma cells. Cancer Res, 2013, Jan 1;73(1):297-306.
[3] Vehlow A, Cordes N. Invasion as target for therapy of glioblastoma multiforme. Biochim Biophys Acta, 2013 Jul 24. doi:pii: S0304-419X(13)00038-3. 10.1016/j.bbcan.2013.07.001. [Epub ahead of print]
[4] Eke I, Zscheppang K, Dickreuter E, Hickmann L, Mazzeo E, Unger K, Krause M, Cordes N. Simultaneous ß1 integrin-EGFR targeting and radiosensitization of human head and neck cancer. J Natl Cancer Inst, 2015 Feb 5;107(2)
[5] Steglich A, Vehlow A, Eke I, Cordes N. α integrin targeting for radiosensitization of three-dimensionally grown human head and neck squamous cell carcinoma cells. Cancer Lett, 2015 Feb 28;357(2):542-8
[6] Dickreuter E, Eke I, Krause M, Borgmann K, van Vugt MA, Cordes N. Targeting of beta1 integrins impairs DNA repair for radiosensitization of head and neck cancer cells. Oncogene, 2015 Jun 15. doi: 10.1038/onc.2015.212. [Epub ahead of print]

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Evaluation study of in-beam PET performances with a Carbon ion linac (CABOTO)
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Purpose: In-Beam PET is a *well-established* method for dose monitoring in hadrontherapy, but its effectiveness is still limited by the accelerator duty cycle [1]. CABOTO [2, 3], CArbon BOoster for Therapy in Oncology, is an innovative development project of an efficient high-frequency linac for hadrontherapy that can accelerate ^{12}C ions and H_2 molecules up to 430 MeV/u, bunched in pulses of the order of 2-5 µs with a repetition rate of 360 Hz.
Thanks to its low duty cycle (less than 0.1%), CABOTO allows the γ-pair acquisition with PET during 99.9% of the treatment time. The main goal of this research is to describe how the CABOTO time-structure influences the in-beam PET images, reconstructed by acquiring the γ-coincidences during the irradiation time as well as in a period following it.
Methods and Materials: The study has been carried out performing several simulations with the FLUKA Monte Carlo code [4, 5] together with MATLAB routines written to take into account analytically the CABOTO time structure.
In a first set of simulations, the $ß^+$ emitter isotopes, produced by the interaction of a pencil beam (protons and ^{12}C-ions) with a water phantom, are identified. Due to the special time structure, the PET detector is sensitive also to γ-pair produced in the $ß^+$-decays of isotopes having half-lives ($T_{1/2}$) in the ms range; the most relevant ones are ^{13}O ($T_{1/2}$=8.6 ms), ^{12}N ($T_{1/2}$=11 ms), ^{9}C ($T_{1/2}$=126.5 ms), ^{8}B ($T_{1/2}$=770 ms). Considering the CABOTO time structure and the acquisition time window as defined before, the $ß^+$ activity versus time has been extrapolated for all $ß^+$ emitters.
A second set of simulations including a PET detector has been carried out, using a modified version of the routines originally developed in Fluka for conventional PET [6]. Arrival times of gamma pair coincidences on the PET detector have been scored and analysed in order to verify their correspondence to the beam irradiation profile. The history of each coincidence has been traced in order to identify the parent isotope, which helps to discriminate and evaluate the true signal versus the background noise. Based on this information, the PET images could be reconstructed from the true coincidences from both the online and offline signal, and quantify the differences.
Results & Conclusions: This work describes the results obtained in the study of the influence of CABOTO time structure on the PET scanner reconstruction. The $ß^+$ activity collected during the irradiation with a single pencil beam has been computed together with the estimated background during the irradiation. The effect of the very short half-life $ß^+$ emitters, which produce positrons of longer ranges, has been studied. Preliminary results obtained in a simulation on a real patient case, with all the beam spots delivered with the correct time structure, are also presented.

Keywords: in-beam PET, hadrontherapy, Monte Carlo

References:

[1] G. Sportelli et al., *First full-beam PET acquisitions in proton therapy with a modular dual-head dedicated system*, Phys. Med. Biol. 59 (2014) 43-60
[2] U. Amaldi, S. Braccini, P. Puggioni, *High Frequency Linacs for Hadrontherapy*, RAST 2 (2000) 111
[3] S. Verdú-Andrés, U. Amaldi ,Á. Faus-Golfe, *CABOTO, a high-gradient linac for hadrontherapy, J. of Radiation Research, 2013, 54, i155–i161*
[4] T.T. Bohlen, F. Cerutti, M.P.W. Chin, A. Fasso`, A. Ferrari, P.G. Ortega,
A. Mairani, P.R. Sala, G. Smirnov, and V. Vlachoudis, *The FLUKA Code: Developments and Challenges for High Energy and Medical Applications*
Nuclear Data Sheets 120, 211-214 (2014)
[5] A. Ferrari, P.R. Sala, A. Fasso`, and J. Ranft *FLUKA: a multi-particle transport code*, CERN-2005-10 (2005), INFN/TC_05/11, SLAC-R-773
[6] P. G. Ortega, T. T. Boehlen, F. Cerutti, M. P. W. Chin, A. Ferrari, A. Mairani, C. Mancini, P. R. Sala & V. Vlachoudis, *A dedicated tool for PET scanner simulations using FLUKA*, 3rd International Conference on Advancements in Nuclear Instrumentation Measurement, Methods and their Applications (ANIMMA), 2013.

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Nanox™: A new multiscale theoretical framework to predict cell survival in the context of particle therapy

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The number of facilities that offer tumor treatment with particle therapy has been increasing substantially over the past decades. The dose distribution deposited by ions, and for the heaviest, their higher biological effectiveness, make them more interesting to destroy localized tumors while sparing healthy tissues. Such an effectiveness is quantified through the RBE (relative biological effectiveness), which is a complex function of multiple parameters like cell line, cell cycle stage, radiation quality and irradiation conditions. Therefore, determining the value of RBE for every scenario is a challenging task that requires modeling to comply with the demands of a clinical environment.
Several solutions have already been developed and a few are currently used in treatment planning [1-4]. Nevertheless, despite the progress these models have allowed, they present some shortcomings [5-7] that may limit their improvement. We present thereby a new approach that gathers some principles of the existing ones and addresses some of their weaknesses. The innovative features of Nanox™ are that it is fully based on statistical physics, taking in particular into account the fluctuations in energy deposition at multiple scales, and that it introduces the concept of a chemical dose. The latter is chosen as a parameter defined at the cell scale to represent the induction of cell death by "non-local" events as the accumulation of cellular oxidative stress or sub-lethal lesions induced by the produced radical species. Such "non-local" events are complementary to the so-called "local" events, which take place at a very localized (nanometric) scale. The "local" events are considered as lethal since a single event can cause cell death.
The cell survival predicted by Nanox™ for V79 cell line was compared with experimental results for photons, protons and carbon ions, and even others like neon and argon ions. A good agreement was found in all cases. In particular, the model is able to describe the effectiveness of ions, including the overkill effect at higher LET values. Moreover, Nanox™ can reproduce the typical shoulder in cell survival curves. This was possible due to the introduction of the "non-local" events, through the chemical dose, which varies with LET. It is worthwhile to note that such results were obtained through the adjustment of a reduced number of free parameters.
The first results of Nanox™, obtained for V79 cell line, give us confidence that this model has potential for application in a clinical scenario in the context of particle therapy. Although it requires the tuning of only a few free parameters, Nanox™ is based on solid principles and a thorough mathematical implementation, which renders this approach simple but reliable for application in clinical practice.

Keywords: RBE; multiscale dosimetry; oxidative stress

References:
[1] Krämer M, Scholz M. Treatment planning for heavy-ion radiotherapy: calculation and optimization of biologically effective dose. Phys Med Biol 2000;45(11):3319–30. doi:10.1088/0031-9155/45/11/314.
[2] Krämer M, Scifoni E, Waelzlein C, et al. Ion beams in radiotherapy – from tracks to treatment planning. J Phys Conf Ser 2012;373:012017.
doi:10.1088/1742-6596/373/1/012017.
[3] Endo M, Koyama-Ito H, Minohara Si, et al. HIPLAN – a heavy ion treatment planning system at HIMAC. J JASTRO 1996;8(3):231–8. doi:10.11182/jastro1989.8.231.
[4] Mizota M, Kanai T, Yusa K, et al. Reconstruction of biologically equivalent dose distribution on CT-image from measured physical dose distribution of therapeutic beam in water phantom. Phys Med Biol 2002;47(6):935–45. doi:10.1088/0031-9155/47/6/306.
[5] Schardt D, Elsässer T, Schulz-Ertner D. Heavy-ion tumor therapy: Physical and radiobiological benefits. Rev Mod Phys 2010;82(1):383–425. doi:10.1103/RevModPhys.82.383.
[6] Beuve M. Formalization and theoretical analysis of the local effect model. Radiat Res 2009;172(3):394–402. doi:10.1667/RR1544.1.
[7] Russo G, Attili A, Bourhaleb F, et al. Analysis of the reliability of the local effect model for the use in carbon ion treatment planning systems. Radiat Prot Dosim 2011;143(2-):497–502. doi:10.1093/rpd/ncq407.

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Expert knowledge and data-driven Bayesian Networks to predict post-RT dyspnea and 2-year survival

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Purpose: The advent of personalized medicine in radiotherapy (RT) is accompanied by the need for accurate outcome prediction. The current state of predictions made by physicians for patient survival and toxicity after lung radiotherapy is comparable to flipping a coin (Oberije et al.,Radiother. Oncol. 2014). In order to assess the value of expert knowledge in prediction modelling (rather than directly predicting outcomes), expert-based and data-driven prediction models were built and compared. Models for two endpoints were created: 2-year survival in NSCLC non-surgery patients and severe dyspnea (CTCAE dyspnea scores ≥ 2) after RT.
Materials/methods: Data from lung cancer patients (994 for dyspnea, 452 for 2-year survival) treated in clinical routine were collected. 10 experts (4 experts participated for both endpoints) selected causal links between patient, disease, treatment, and dose-related variables (19 for dyspnea, 17 for 2-year survival) and the two outcomes. The selected links were used to construct Bayesian Networks (BN) for a comparison with BNs based on a data-driven algorithm. These models were then learned on 80% and validated on 20% of the patient data. Discrimination in the validation data sets is assessed by the Area under the Curve (AUC).